Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc. Open access under CC BY-NC-ND license.

Vol. 63, No. 1, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.09.017

Cardiac Imaging

Short-Term Rosuvastatin Therapy for Prevention of Contrast-Induced Acute Kidney Injury in Patients With Diabetes and Chronic Kidney Disease

Yaling Han, MD, PHD,* Guoying Zhu, MD,† Lixian Han, MD,‡ Fengxia Hou, MD,§ Weijian Huang, MD,‖ Huiliang Liu, MD,¶ Jihong Gan, MD,# Tiemin Jiang, MD,** Xiaoyan Li, MD,†† Wei Wang, MD,‡‡ Shifang Ding, MD,§§ Shaobin Jia, MD,‖‖ Weifeng Shen, MD,¶¶ Dongmei Wang, MD,## Ling Sun, MD,*** Jian Qiu, MD,††† Xiaozeng Wang, MD,* Yi Li, MD,* Jie Deng, MD,* Jing Li, MD,* Kai Xu, MD,* Bo Xu, MBBS,‡‡‡ Roxana Mehran, MD,§§§ Yong Huo, MD‖‖‖

Shenyang, Wuhan, CangZhou, Changchun, Wenzhou, Beijing, Wulumuqi, Tianjin, Jinan, Guangzhou, Yinchuan, Shanghai, Shijiazhuang, and Fushun, China; and New York, New York

Objectives This study sought to evaluate the safety and efficacy of rosuvastatin in preventing contrast-induced acute kidney injury (CI-AKI) in patients with diabetes mellitus (DM) and chronic kidney disease (CKD).

Background CI-AKI is an important complication after contrast medium injection. While small studies have shown positive results with statin therapy, the role of statin therapy in prevention of CI-AKI remains unknown.

Methods We randomized 2,998 patients with type 2 DM and concomitant CKD who were undergoing coronary/peripheral arterial angiography with or without percutaneous intervention to receive rosuvastatin, 10 mg/day (n = 1,498), for 5 days (2 days before, and 3 days after procedure) or standard-of-care (n = 1,500). Patients' renal function was assessed at baseline, 48 h, and 72 h after exposure to contrast medium. The primary endpoint of the study was the development of CI-AKI, which was defined as an increase in serum creatinine concentration ≥0.5 mg/dl (44.2 μmol/l) or 0.25% above baseline at 72 h after exposure to contrast medium.

Results Patients randomized to the rosuvastatin group had a significantly lower incidence of CI-AKI than controls (2.3% vs. 3.9%, respectively; p = 0.01). During 30 days' follow-up, the rate of worsening heart failure was significantly lower in the patients treated with rosuvastatin than that in the control group (2.6% vs. 4.3%, respectively; p = 0.02).

Conclusions Rosuvastatin significantly reduced the risk of CI-AKI in patients with DM and CKD undergoing arterial contrast medium injection. (Rosuvastatin Prevent Contrast Induced Acute Kidney Injury in Patients With Diabetes [TRACK-D]; NCT00786136) (J Am Coll Cardiol 2014;63:62–70) © 2014 by the American College of Cardiology Foundation

Open access under CC BY-NC-ND license.

Contrast-induced acute kidney injury (CI-AKI) is a major complication with adverse outcomes after contrast medium injection (1). Although the risk of developing CI-AKI is low in patients with normal renal function, it is dramatically

See page 80

From the *Department of Cardiology, Shenyang Northern Hospital, Shenyang, China; †Department of Cardiology, WuHan Asia Heart Hospital, Wuhan, China; ‡Department of Cardiology, CangZhou Central Hospital, CangZhou, China; §Department of Cardiology, Changchun Central Hospital, Changchun, China; ‖Department of Cardiology, The First Affiliated Hospital of Wenzhou Medical College, Wenzhou, China; ¶Department of Cardiology, General Hospital of Armed Police Forces, Beijing, China; #Department of Cardiology, Lanzhou Military WuluMuqi PLA Hospital, Wulumuqi, China; **Department of Cardiology, Affiliated Hospital of Medical College of Armed Police Forces, Tianjin, China; ††Department of Cardiology, Jinan Military General Hospital, Jinan, China; ‡‡Department of Cardiology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; §§Department of Cardiology, Wuhan General Hospital of Guangzhou Military, Wuhan, China; ‖‖Department of Cardiology, Affiliated Hospital of Ningxia Medical College, Yinchuan, China; ¶¶Department of Cardiology, Ruijin Hospital Affiliated to the Medical College of Shanghai Jiaotong University, Shanghai, China; ##Department of Cardiology, Shijiazhuang International Peace Hospital, Shijiazhuang, China; ***Department of Cardiology, Fushun Central Hospital, Fushun, China; †††Department of Cardiology, General Hospital of Guangzhou Military Command of PLA, Guangzhou, China; ‡‡‡Cardiac Catheterization Laboratory, Fuwai Hospital, Beijing, China; §§§Zena and Michael A. Weiner Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; and the ‖‖‖Department of Cardiology, First Hospital of Beijing University, Beijing, China. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 15, 2013; revised manuscript received September 3, 2013, accepted September 5, 2013.

higher in patients with conditions such as diabetes mellitus (DM) or chronic kidney disease (CKD) (2,3). Therefore, strategies to prevent CI-AKI in DM patients with CKD are urgently needed.

CI-AKI mechanisms are complex but may be related to direct renal tubular toxicity, vasoconstriction, and high oxidative stress. Statins have beneficial effects on endothelial function, nitric oxide production, and oxidative stress, which are directly related to the development of CI-AKI (4,5). Statins have renoprotective effects in patients with CKD (6,7). However, results for the efficacy of statin therapy to prevent CI-AKI in high-risk patients are inconsistent, mostly because of small sample sizes (8–15). Despite this, the latest European Society of Cardiology guidelines on myocardial revascularization advise the use of statins to prevent CI-AKI, especially in high-risk patients (16).

The purpose of this clinical trial was to examine the effects of short-term rosuvastatin therapy on the incidence of CI-AKI in a multicenter, prospective trial in patients with DM and with mild-to-moderate CKD undergoing coronary/peripheral arterial diagnostic angiography, left ventriculography, or percutaneous coronary intervention (PCI).

Methods

Study population. This study was an investigator-initiated, prospective, randomized, controlled, multicenter clinical trial performed in China, designed by the steering committee and registered at Clinicaltrials.gov (NCT00786136). Patients with DM and CKD undergoing coronary/peripheral arterial diagnostic angiography, left ventriculography, or PCI were eligible.

The primary objective was to evaluate the safety and efficacy of statin therapy for prevention of CI-AKI in patients with DM and CKD exposed to contrast medium. The trial included patients 18 to 75 years of age with type 2 DM and concomitant stage 2 or 3 CKD who had not received any statin treatment for at least 14 days and in whom metformin or aminophylline had been withdrawn for at least 2 days prior to contrast medium administration (Fig. 1). Exclusion criteria were hypersensitivity to contrast medium or statins, type 1 DM, ketoacidosis, lactic acidosis, stage 0 or 1 CKD, stage 4 or 5 CKD, acute ST-segment elevation myocardial infarction (STEMI) within the previous 4 weeks, class IV heart failure as defined by the New York Heart Association (NYHA) functional classification system, hemodynamic instability, administration of iodinated contrast medium during the 2 weeks before randomization, low-density lipoprotein cholesterol (LDL-C) concentration <1.82 mmol/liter, hepatic dysfunction (serum alanine-aminotransferase [ALT] concentration 3 times greater than the upper limit of normal), thyroid insufficiency, or renal artery stenosis (unilateral >70% or bilateral >50%).

The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine (sCr) concentrations by using the modified glomerular filtration rate estimating equation for Chinese patients with CKD (17): eGFR (ml/min/1.73 m^2) = $175 \times (sCr)^{-1.234} \times (age)^{-0.179}$ (0.79 if female).

Abbreviations and Acronyms

CI-AKI = contrast-induced acute kidney injury

CKD = chronic kidney disease

DM = diabetes mellitus

eGFR = estimated glomerular filtration rate

hsCRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

sCr = serum creatinine

STEMI = ST-segment elevation myocardial infarction

TC = total cholesterol

Study protocol. The study was approved by the Ethics Committee of Shenyang Northern Hospital. All patients provided written informed consent before enrollment. Block randomization was performed using computerized open-label assignment by blinded envelopes, used in a consecutive fashion, with a block size of 6. Patients were randomized to receive either rosuvastatin (Crestor, AstraZeneca, London, United Kingdom), 10 mg every evening, from 2 days before to 3 days after contrast medium administration (total dose of 50 mg of rosuvastatin over 5 days) or to a control group. Patients assigned to the control group did not receive any statins. Statin therapy was resumed in both groups 3 days after contrast medium administration, following completion of the study endpoints.

Hydration therapy was standard and administered at the physician's discretion and included isotonic saline (0.9% sodium chloride, 1 ml/kg/h) started 12 h before and continued for 24 h after contrast medium administration. The iso-osmolar, nonionic contrast medium iodixanol (320 mg iodine/ml, Visipaque, GE Healthcare, Piscataway, New Jersey) was administered during all procedures.

Blood samples were taken to measure sCr concentrations before randomization and at 48 h and 72 h after contrast medium administration. The peak post-procedural sCr value was used for the primary endpoint evaluation. Renal function was measured using eGFR in all patients. Type 2 DM was diagnosed using the criteria of the American Diabetes Association (18). Levels of high-sensitivity C-reactive protein (hsCRP), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were also measured using commercial kits on the day of admission and 3 days after the procedure. Urinary albumin excretion was assessed by measurement of urinary concentrations of albumin and creatinine (albumin/creatinine ratio [ACR]) in urine samples collected on the morning of the day before randomization and 3 days after the procedure. Urinary albumin concentrations were measured using the immunoturbidimetry method.

Endpoints and definitions. The primary endpoint was the development of CI-AKI, defined as an increase in sCr concentration ≥0.5 mg/dl (44.2 μmol/l) or ≥25% above baseline at 72 h after exposure to the contrast medium. Clinical outcomes included events occurring within 30 days after contrast: 1) all-cause death; 2) dialysis or hemofiltration due to symptoms or signs of uremic syndrome or management of refractory hypervolemia,

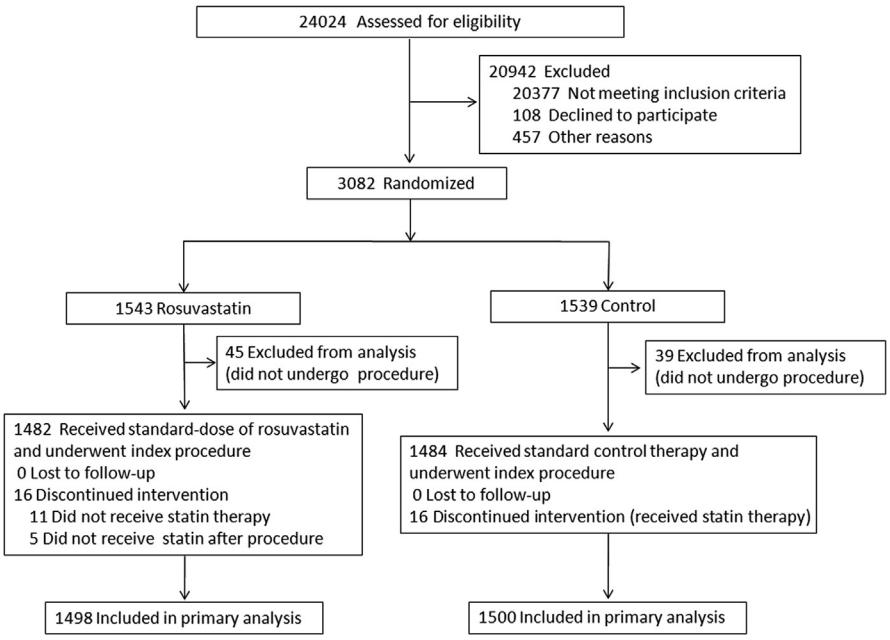

Figure 1 Patient Flowchart

hyperkalemia, or acidosis (19); or 3) worsening heart failure, defined as a deteriorated NYHA functional class (class change ≥1).

All patients had a follow-up evaluation at a clinic visit or via telephone contact at 30 days. The China Cardiovascular Research Foundation (CCRF), an independent clinical research organization, was responsible for database management, safety monitoring, and adverse event evaluation. All adverse events were adjudicated by a blinded, independent clinical events committee. The CCRF reviewed the data periodically to identify any potential safety issues.

Statistical analysis. Sample size calculation was performed by assuming a 10% incidence of the primary endpoint in the control group and a 30% reduction in the treatment arm. From these assumptions, 2,712 patients were required (1,356 per group) from which to detect a 30% relative reduction in the incidence of the primary endpoint in the treatment arm with 80% power and a 2-sided significance level of 5%.

Statistical analysis was based on the modified intention-to-treat populations and performed using SAS version 9.13 software (SAS Institute Inc., Cary, North Carolina). Comparisons among normally distributed continuous variables, expressed as mean ± SD, were performed using Student *t* tests; non-normally distributed continuous variables, presented as medians and interquartile ranges, were analyzed using Wilcoxon rank-sum tests. The chi-square or Fisher exact test was used for categorical data, expressed as percentages. Logistic regression analysis was used to calculate odds ratios for the comparison of CI-AKI rates between groups. All p values were 2-tailed, and statistical significance was defined by a p value ≤0.05. All statistical analyses were performed by the CCRF.

Results

Between December 2008 and October 2011, 3,082 patients were enrolled at 53 centers in China. Eighty-four patients did not undergo angiography and were excluded. In total, 2,998 patients were included: 1,498 patients were allocated to the rosuvastatin group and 1,500 to the control group. Among all patients, 1,751 (58.4%) were statin-naive, and 1,247 (41.6%) had not taken statins for at least 14 days due to poor compliance or other reasons but had previously used statins. Thirty-two patients (1.07%) deviated from the protocol: in the rosuvastatin group, 11 patients did not receive statin therapy at all, and 5 did not receive a statin after contrast medium administration; in the control group, 16 patients received statin therapy (1.1%).

Baseline clinical characteristics were well balanced between groups (Table 1). Of the 2,998 patients, 85.9% underwent diagnostic coronary angiography and left ventriculography (n = 2,575), 13.5% diagnostic coronary/peripheral angiography and left ventriculography (n = 405), 0.6% peripheral angiography (n = 18), 53% PCI (n = 1,589), and 1% percutaneous peripheral intervention (n = 30) (Table 2). There were no significant differences between maximum sCr levels and minimum eGFR values for all patients, minimum eGFR values for patients with stage 2

Table 1 Baseline Patient Characteristics

Variable	Rosuvastatin Group (n = 1,498)	Control Group (n = 1,500)	p Value
Age (yrs)	61.45 ± 8.64	61.44 ± 8.64	0.97
Weight (kg)	72.32 ± 10.42	72.88 ± 10.29	0.14
Height (cm)	168.33 ± 7.81	168.52 ± 7.64	0.52
Male	963 (64.3)	991 (66.1%)	0.31
Smoking	463 (30.9)	491 (32.7)	0.17
Family history of coronary heart disease	112 (7.5)	104 (6.9)	0.57
History of statin use			0.85
Statin-naive	878 (58.6)	873 (58.2)	
Previous statin use	620 (41.4)	627 (41.8)	
Anemia status*			0.59
No anemia	1,337 (91.3)	1,344 (91.9)	
Anemia	127 (8.7)	118 (8.1)	
Diabetes history			0.95
≤5 yrs	831 (55.5)	840 (56.0)	
>5 yrs and <10 yrs	284 (18.9)	283 (18.9)	
≥10 years	383 (25.6)	377 (25.1)	
Hypertension	1,066 (71.3)	1090 (72.7)	0.39
Hypertriglyceridemia	139 (9.3)	117 (7.8)	0.15
TIA/stroke	188 (12.6)	208 (13.9)	0.28
Congestive heart failure	228 (15.2)	237 (15.8)	0.66
Peripheral vascular disease	45 (3.0)	37 (2.5)	0.37
History of liver disease	34 (2.3)	24 (1.6)	0.18
Prior myocardial infarction	322 (21.5)	296 (19.7)	0.24
Myocardial ischemia			0.09
None	227 (15.1)	267 (17.8)	
Silent myocardial ischemia	12 (0.8)	12 (0.8)	
Stable angina	76 (5.1)	95 (6.3)	
Unstable angina	1,071 (71.5)	1,005 (67.0)	
NSTEMI	112 (7.5)	121 (8.1)	
Medications			
Aspirin	1,397 (93.3)	1,419 (94.6)	0.127
ACEI	981 (65.5)	947 (63.3)	0.20
ARB	363 (24.2)	353 (23.6)	0.67
Beta-blocker	1,224 (81.7)	1,201 (80.2)	0.30
Insulin	486 (32.4)	457 (30.5)	0.254
Diuretic	321 (21.4)	329 (22.0)	0.72
Calcium antagonist	624 (41.7)	614 (41.0)	0.70
Heparin	923 (61.6)	944 (63.0)	0.44
Digitalis	132 (8.8)	131 (8.7)	0.95
Vitamin C	25 (1.7)	29 (1.9)	0.59
Dopamine	23 (1.5)	22 (1.5)	0.88
Sodium bicarbonate	21 (1.4)	26 (1.7)	0.46
Hydration	673 (44.9)	642 (42.8)	0.25
LVEF, %	62.27 ± 8.87	61.96 ± 8.91	0.42
NYHA functional classification			0.54
I	1,152 (76.9)	1,149 (76.6)	
II	302 (20.2)	318 (21.2)	
III	44 (2.9)	33 (2.2)	
Laboratory determinations:			
Total cholesterol (mg/dl)	177.88 ± 46.02	177.11 ± 45.24	0.67
LDL-C (mg/dl)	98.61 ± 31.71	97.45 ± 30.55	0.35
Fasting glucose (mg/dl)	134.07 ± 51.18	132.81 ± 49.37	0.48
BMI (kg/m^2)	25.49 ± 3.01	25.64 ± 2.93	0.16

Continued in the next column

*Values are mean ± SD or n (%). Definition of anemia = hemoglobin concentration <120 g/l in males or <110 g/l in females.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; NSTEMI = non-ST segment elevation myocardial infarction; NYHA = New York Heart Association; TIA = transient ischemic attack.

CKD, minimum eGFR values for patients with stage 3 CKD, and ACR after contrast medium administration in the rosuvastatin and control groups.

The incidence of CI-AKI was lower in the rosuvastatin-treated group (2.3% vs. 3.9%, p = 0.01) (Fig. 2). In the subgroup of patients with stage 2 CKD, the incidence of CI-AKI was 1.5% in the rosuvastatin group compared with 3.3% in controls (p = 0.01). On the basis of these results, 62.5 patients would need to be treated (NNT) with rosuvastatin for 5 days to prevent the occurrence of one case of CI-AKI.

There were no significant differences in all-cause deaths (rosuvastatin vs. controls, 0.2% vs. 0.3%, respectively; p = 0.73) or dialysis/hemofiltration (0% vs. 0.1%, respectively; p = 0.50) (Table 3). The incidence of worsening heart failure was significantly decreased following rosuvastatin treatment (2.6% vs. 4.3%, respectively; p = 0.02).

Multivariable analysis (Table 4) revealed that rosuvastatin and hemoglobin were independently associated with a decreased risk of CI-AKI. Independent predictors of CI-AKI included baseline acute coronary syndrome (ACS), NYHA functional classification, and a decreased eGFR (<60 ml/min/1.73 m^2). The benefit of rosuvastatin therapy was consistently effective among various subgroups (Fig. 3). Both statin-naive and non-naive patients showed a similar trend toward receiving benefit from rosuvastatin against the occurrence of CI-AKI (Table 5). An interaction test showed that statin history had no effect on CI-AKI occurrence in the present study (p = 0.776).

There were no significant differences between the 2 groups at baseline in TC (177.88 ± 46.02 mg/dl vs. 177.11 ± 45.24 mg/dl, rosuvastatin vs. controls, respectively; p = 0.67), LDL-C (98.61 ± 31.71 mg/dl vs. 97.45 ± 30.55 mg/dl, respectively; p = 0.35), and hsCRP levels (0.40 mg/l; interquartile range: 0.20 to 1.10 vs. 0.40 mg/l, respectively; interquartile range: 0.20 to 0.90; p = 0.95). Follow-up TC (151.20 ± 37.90 mg/dl vs. 182.91 ± 39.83 mg/dl, respectively; p < 0.01), LDL-C (81.59 ± 25.91 mg/dl vs. 100.16 ± 24.75 mg/dl, respectively; p < 0.01), and hsCRP levels (0.40 mg/l; interquartile range: 0.20 to 0.93 vs. 0.50 mg/l; interquartile range: 0.20 to 1.10 mg/l, respectively; p = 0.01) were

Table 2 Biochemical and Procedural Characteristics

Variable	Rosuvastatin Group (n = 1,498)	Control Group (n = 1,500)	p Value
Peripheral vascular angiography	219 (14.6)	205 (13.7)	0.45
Coronary diagnostic angiography			0.17
Normal	148 (10.1)	142 (9.8)	
Single-vessel disease	330 (22.5)	367 (25.4)	
Multi-vessel disease	991 (67.4)	935 (64.8)	
Percutaneous coronary intervention	808 (53.9)	782 (52.1)	0.32
Percutaneous peripheral intervention	15 (1.0)	16 (1.1)	0.86
Serum creatinine (μmol/l)			
Baseline	95.08 ± 22.92	94.95 ± 20.84	0.88
Maximal post-procedural value	95.12 ± 25.39	95.71 ± 29.01	0.55
eGFR (ml/min/1.73 m^2)			
All patients at baseline	74.16 ± 14.99	74.43 ± 15.24	0.62
Stage 2 CKD at baseline	78.46 ± 11.37	78.99 ± 11.27	0.24
Stage 3 CKD at baseline	50.20 ± 8.90	49.56 ± 8.70	0.43
Microalbuminuria (mg/dl)			
Baseline	29.83 ± 46.60	30.89 ± 44.65	0.63
Post-procedural	24.18 ± 39.38	25.60 ± 42.32	0.47
ACR			
Baseline	0.22 ± 1.82	0.13 ± 1.02	0.23
Post-procedural	0.18 ± 1.36	0.15 ± 1.06	0.68
Median contrast agent dose, ml	120 (100–200)	110 (100–200)	0.10

Values are n (%), mean ± SD, or median (interquartile range).
ACR = urinary albumin/creatinine ratio; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

significantly lower with rosuvastatin. Furthermore, post-procedural hsCRP levels were higher in patients with CI-AKI (1.40 mg/l; interquartile range: 0.60 to 4.90 mg/l vs. 0.40 mg/l; interquartile range: 0.20 to 1.00 mg/l, respectively; p = 0.0054).

Considering all patients, 7 developed both CI-AKI and worsening heart failure, 85 developed CI-AKI only, and 96 developed worsening heart failure only, whereas 2,810 patients did not develop either of the 2 (McNemar test: p = 0.226), suggesting that the effects of rosuvastatin on cardiac function were independent of changes in renal function. Baseline hemoglobin levels were lower and prevalence of anemia was higher in patients who developed CI-AKI (all: p < 0.05) (Table 6).

There were no significant differences between the 2 groups in the rates of muscle pain, liver function tests results, gastrointestinal disorders, or incidence of edema or rash.

Discussion

This is the first large randomized, multicenter, prospective study to evaluate the safety and efficacy of statin therapy for the prevention of CI-AKI in DM patients with mild-to-moderate CKD. In this trial, we observed that periprocedural administration of rosuvastatin, 10 mg daily for a short duration (5 days), reduced the incidence of

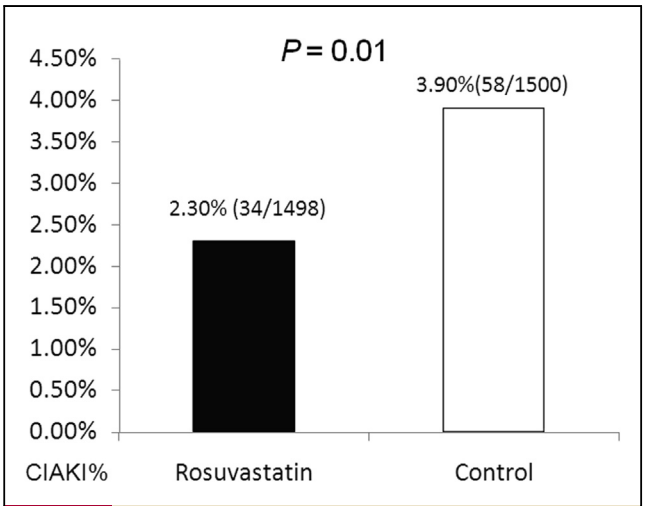

Figure 2 Primary Endpoint: CI-AKI Occurrence

The incidence of the primary endpoint was significantly lower in the rosuvastatin group than in the control group (2.3% vs. 3.9%, p = 0.01).

CI-AKI in patients with type 2 DM and CKD, suggesting that a short course of oral statin may reduce the incidence of CI-AKI after contrast medium injection in these patients. These results are of clinical significance because CI-AKI is a severe complication in patients with already impaired kidney function.

We also evaluated incremental risk factors in these high-risk patients for CI-AKI development and observed that ACS, NYHA functional classification, anemia and decreased eGFR were independent correlates of CI-AKI, consistent with previous studies (20,21). Because these risk factors can be easily identified, prophylactic measures for the prevention of CI-AKI should be considered in these patients.

A recent study showed that statin was useful in preventing acute kidney injury following cardiovascular surgery (22). Furthermore, several studies reported that statins may be effective in preventing CI-AKI (11,23). However, the present study is the first to evaluate the preventive effect of rosuvastatin, a potent LDL-C-lowering statin, on the development of CI-AKI in DM patients with concomitant CKD who have a high CI-AKI risk. Notably, the sample size of the present study, almost 3,000 DM patients with mild-to-moderate CKD, afforded the statistical power to evaluate differences between statin and no-statin treatment, and to explore the risk factors associated with CI-AKI in this population. In current clinical practice, many patients with cardiovascular disease do not use statins (24). Our results show that rosuvastatin can significantly reduce the risk of CI-AKI, even in patients with normal lipid levels. Therefore, the present study indicated that in addition to hydration, statin should be given to all patients with DM and mild CKD who are receiving contrast medium.

The incidence of CI-AKI in the control group (3.9%) was lower than anticipated from our sample size calculation

Table 3 Clinical 30-Day Follow-Up After Contrast Medium Administration

Variables	Rosuvastatin Group (n = 1,498)	Control Group (n = 1,500)	p Value
All-cause deaths	3 (0.2)	5 (0.3)	0.73
Dialysis/hemofiltration	0 (0.0)	2 (0.1)	0.50
Worsening heart failure*	39 (2.6)	64 (4.3)	0.02

*Values are n (%). Defined by change of New York Heart Association classification (class change ≥ 1).

(10%), which was based on CI-AKI rates from prior studies. In our study, patients with stages 4 and 5 CKD were excluded and a majority (85%) had stage 2 CKD, in contrast to findings of previous studies that enrolled patients with stage 3 to 4 CKD. Furthermore, it was recommended that patients be well hydrated prior to their procedure, which could have decreased the rate of CI-AKI. The median volumes of the contrast medium administered in our study (120 ml in the rosuvastatin group and 110 ml in controls) were less than the volumes administered in previous studies (ranging from 173 to 234 ml) (11,15), which suggested that lowering contrast volume by any measure could prevent CI-AKI in patients with mild CKD. Despite a lower incidence of CI-AKI in the control group, rosuvastatin treatment showed a 42% relative risk reduction in CI-AKI.

In the subgroup analysis, the beneficial effects of rosuvastatin were manifest mainly in patients with stage 2 CKD. Current clinical practice does not recommend prevention of CI-AKI in patients with mild CKD. However, even small increases in serum creatinine can be associated with worse clinical outcomes, increasing short- and long-term mortality independently from baseline sCr values (25,26). Subgroup analysis also showed that rosuvastatin was less effective in patients with anemia. Patients with lower hemoglobin may have iron deficiency or inadequate receptors to erythropoietin. The outer medullary region in the kidney is particularly susceptible to ischemic injury (27), and contrast medium could increase oxygen affinity of hemoglobin, and oxygen delivery to the peripheral tissues might be impaired (28), resulting in CI-AKI. Anemia is common among patients with kidney disease and results from decreased red blood cell survival, toxic inhibitors of erythropoiesis, and deficiency in iron and folate (29). Hemoglobin levels were not available after the procedure. However, our results showed that baseline hemoglobin levels were lower in patients who developed CI-AKI and that the prevalence of anemia was higher. The JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) study showed that rosuvastatin increased hemoglobin levels in patients with anemia and low-grade inflammation (30).

Table 4 Multivariable Analysis for CI-AKI Predictors of CI-AKI

Variable	OR	95% CI	p Value
Rosuvastatin	0.60	(0.39–0.94)	0.03
Male	1.09	(0.67–1.78)	0.73
Age	0.999	(0.973–1.026)	0.94
BMI	0.98	(0.91–1.05)	0.57
ACS	1.86	(1.17–2.95)	0.01
Prior myocardial infarction	0.89	(0.50–1.58)	0.69
Diabetes history	0.92	(0.71–1.20)	0.55
NYHA functional classification	1.61	(1.14–2.29)	0.01
Hemoglobin	0.986	(0.972–0.999)	0.01
eGFR (<60 ml/min/1.73 m^2)	1.77	(1.31–2.40)	<0.01
Contrast agent dose	1.002	(0.999–1.005)	0.12
Hydration	0.83	(0.53–1.31)	0.43
ACEI/ARB	1.15	(0.63–2.10)	0.65
Beta-blocker	0.94	(0.54–1.61)	0.82

ACS = acute coronary syndrome(s); CI-AKI = contrast-induced acute kidney injury. All other abbreviations are as shown in Table 1.

In our study, hydration was performed at the physician's discretion, and not all patients received it (only 44.9% of the rosuvastatin group and 42.8% of the control group) because: 1) 15% of patients had congestive heart failure, and fluid administration in these patients was restricted; and 2) at an early stage of the study, clinical guidelines stated that hydration was not mandatory. With regard to the safety of rosuvastatin, results of the study were consistent with those of previous large-scale randomized studies (6,31). Although there have been reports stating that rosuvastatin increased proteinuria (32,33), treatment at 10 mg per day for 5 days had no effect on proteinuria. A recent study showed that after 104 weeks of treatment with either 80 mg atorvastatin or 40 mg rosuvastatin daily, the rate of abnormal liver enzyme levels was lower with rosuvastatin than with atorvastatin, and that there was no significant difference in the development of renal impairment (31).

The mechanism of statin in CI-AKI prevention remains unknown. In the present study, patients who developed CI-AKI had higher post-procedural hsCRP levels, and the preventive effect of rosuvastatin on CI-AKI development was paralleled by a significant decrease in post-procedural hsCRP levels. Inflammation may contribute to the pathogenesis of CI-AKI, and renal protection by rosuvastatin during exposure to contrast medium could be due to attenuation of inflammatory responses, a phenomenon also observed in the JUPITER trial (34). Direct toxic effects of contrast medium on renal cells are also thought to contribute to the pathogenesis of CI-AKI. A study showed that pretreatment with statin prevented epithelial tubular renal cell apoptosis and increased survival signaling pathways (8). Preventing contrast medium-induced renal cell apoptosis seems to play an important role in statins' effects on CI-AKI occurrence.

We observed that rosuvastatin significantly decreased the incidence of worsening of heart failure, which might be based mainly on the following potential mechanisms (35): 1) attenuation of negative inotropic effects and apoptosis in myocardial cells by reducing inflammatory cytokines; 2) improvement of endothelial function by increasing the production of endothelial nitric oxide; 3) reduction of the

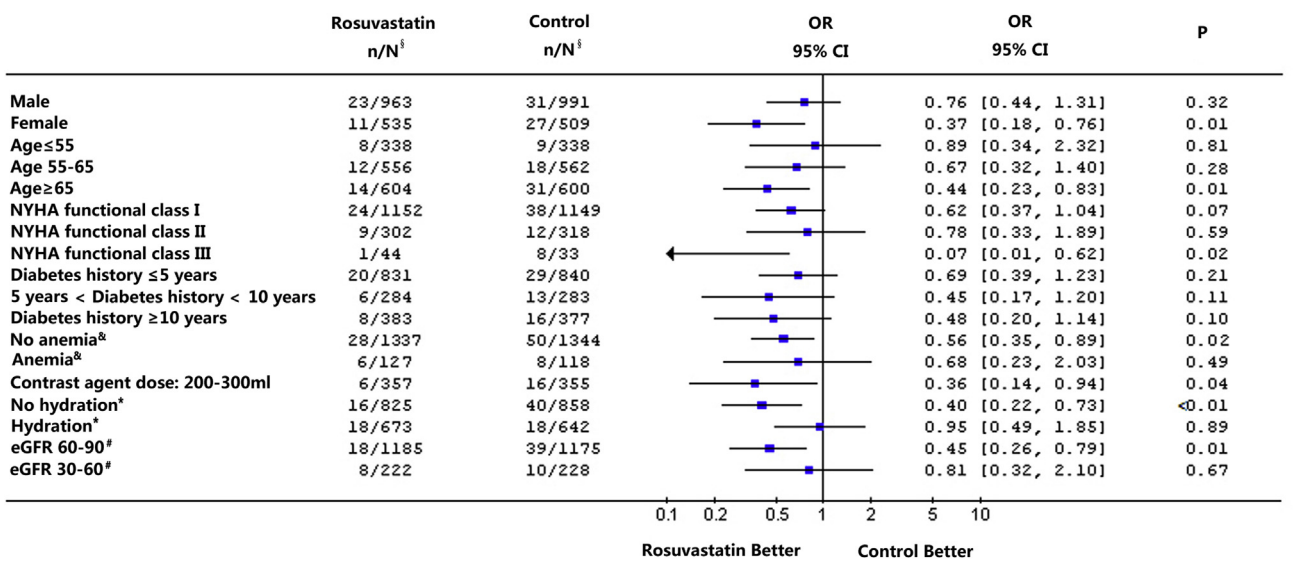

Figure 3 Effects of Rosuvastatin on CI-AKI According to Subgroups

These subgroups are provided as a reference only. §n = number of patients with CI-AKI; N = total number of patients in each subgroup. *There were no interaction effects between rosuvastatin and hydration therapy (p = 0.058) for the incidence of CI-AKI. &Data missing at baseline in 72 patients. #Data missing at baseline in 188 patients. Missing data were due to unprescribed tests at recruitment. CI = confidence interval; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association.

formation of oxygen-derived free radicals; and 4) decreased sympathetic nerve activity in patients with heart failure. However, the exact mechanism by which short-term rosuvastatin treatment decreases the incidence of worsening of heart failure deserves further study.

Indeed, statins are known to exert pleiotropic effects and to decrease systemic inflammation (36), reflected by decreased hsCRP levels (37). Since inflammation is a pathogenic factor of kidney injury (38), decreasing systemic inflammation and hsCRP levels might be part of the mechanism explaining the reduced CI-AKI incidence after rosuvastatin. Because hsCRP is involved in inflammation-mediated decreased endothelial function and vascular injury (35), hsCRP-mediated inflammation might be the link between worsening heart failure and CI-AKI. Furthermore, CRP correlates negatively with eGFR (39), although it is not a unanimous finding (40). In agreement with this possible mechanism, our results showed that short-course rosuvastatin decreased hsCRP levels, decreased CI-AKI incidence, and decreased worsening of heart failure. However, further studies are required to assess the exact mechanisms.

Study limitations. First, the open-label design of the study may have introduced bias. However, all events and biomarkers were collected and adjudicated by a blinded, independent committee. Second, the finding that the beneficial effects of rosuvastatin were not seen in patients with stage 3 CKD was from a subgroup analysis, and a stratified prospective study will be needed in the future. Third, study outcomes may have been affected by the dose of rosuvastatin, which was relatively low (10 mg/day), and mean body mass indexes (BMI) in current Asian population are lower than those in Caucasian populations with type 2 DM and renal disease. Therefore, further studies are needed to explore whether the dosage of rosuvastatin demonstrating benefit is the same for other populations. However, in an analysis of the Michigan Cardiovascular Consortium database, the benefits of statins against CI-AKI in a Caucasian population with a BMI >25 kg/m^2 have been well observed (10). Thus, results from that previous study and from the present study strongly suggest

Table 5 Occurrence of CI-AKI in Statin-Naive and Non-Naive Patients

Statin History	Rosuvastatin Group Naive/Non-Naive (%)	Control Group Naive/Non-Naive (%)	p Value
Statin non-naive	16/628 (2.5%)	27/619 (4.4%)	0.089
Statin-naive	18/870 (2.1%)	31/881 (3.5%)	0.081
All patients	34/1498 (2.3%)	58/1500 (3.9%)	0.01

CI-AKI = contrast-induced acute kidney injury.

Table 6 Hemoglobin Levels and Anemia Prevalence in CI-AKI and Non-CI-AKI Patients

Baseline	CI-AKI Patients (n = 88)	Non-CI-AKI Patients (n = 2,837)	p Value
Baseline hemoglobin (g/l)	129.9 ± 18.0	135.2 ± 15.8	0.002
Anemia	13 (14.8)	231 (8.1)	0.047

CI-AKI = contrast-induced acute kidney injury.

that statins can reduce CI-AKI in Western and Chinese populations, regardless of BMI. Regarding the dose, 10 mg of rosuvastatin was lower than that usually used in Western countries. However, given the fact that plasma exposure to the same dose of rosuvastatin has been observed to be approximately 2-fold higher in Asian populations than in Caucasians (41), the relatively low dosage regimen in the present study might be aligned with the efficacy of higher dosage used in Western countries. In the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) study, 41.5% of patients with DM and CKD conducted at 623 sites in 24 countries were not taking statins at baseline (42), and statin-naive patients may be more prevalent in developing countries, but there is a lack of epidemiological data on this aspect. Of important value, our results provide strong indications that patients with DM and CKD should receive short-term rosuvastatin to prevent CI-AKI, regardless of whether they previously used statins or not. Finally, subgroup analyses provided in Figure 3 are only indicative and cannot be used to make any conclusions. Indeed, the present study was not powered to detect differences among these small groups.

Conclusions

Rosuvastatin at 10 mg per day for 5 days reduces the incidence of CI-AKI in patients with type 2 DM and CKD, who were not already on a statin regimen. A short course of oral statin may reduce the incidence of CIN.

Reprint requests and correspondence: Dr. Yaling Han, Department of Cardiology, Shenyang Northern Hospital, 83 Wenhua Road, Shenyang 110016, China. E-mail: hanyl169@gmail.com.

REFERENCES

1. Solomon R, Dauerman HL. Contrast-induced acute kidney injury. Circulation 2010;122:2451–5.
2. McCullough PA, Adam A, Becker CR, et al. Risk prediction of contrast-induced nephropathy. Am J Cardiol 2006;98:27K–36K.
3. Chen SL, Zhang J, Yei F, et al. Clinical outcomes of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention: a prospective, multicenter, randomized study to analyze the effect of hydration and acetylcysteine. Int J Cardiol 2008;126:407–13.
4. Tumlin J, Stacul F, Adam A, et al. Pathophysiology of contrast-induced nephropathy. Am J Cardiol 2006;98:14K–20K.
5. Giusti-Paiva A, Martinez MR, Felix JV, et al. Simvastatin decreases nitric oxide overproduction and reverts the impaired vascular responsiveness induced by endotoxic shock in rats. Shock 2004;21:271–5.
6. Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C–reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. J Am Coll Cardiol 2010;55:1266–73.
7. Abe M, Maruyama N, Yoshida Y, Ito M, Okada K, Soma M. Efficacy analysis of the lipid-lowering and renoprotective effects of rosuvastatin in patients with chronic kidney disease. Endocr J 2011;58:663–74.
8. Quintavalle C, Fiore D, De Micco F, et al. Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. Circulation 2012;126:3008–16.
9. Patti G, Nusca A, Chello M, et al. Usefulness of statin pretreatment to prevent contrast-induced nephropathy and to improve long-term outcome in patients undergoing percutaneous coronary intervention. Am J Cardiol 2008;101:279–85.
10. Khanal S, Attallah N, Smith DE, et al. Statin therapy reduces contrast-induced nephropathy: an analysis of contemporary percutaneous interventions. Am J Med 2005;118:843–9.
11. Patti G, Ricottini E, Nusca A, et al. Short-term, high-dose atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [atorvastatin for reduction of myocardial damage during angioplasty–contrast-induced nephropathy] trial. Am J Cardiol 2011;108:1–7.
12. Pappy R, Stavrakis S, Hennebry TA, Abu-Fadel MS. Effect of statin therapy on contrast-induced nephropathy after coronary angiography: a meta-analysis. Int J Cardiol 2011;151:348–53.
13. Zhang L, Lu Y, Wu B, et al. Efficacy of statin pretreatment for the prevention of contrast-induced nephropathy: a meta-analysis of randomised controlled trials. Int J Clin Pract 2011;65:624–30.
14. Toso A, Maioli M, Leoncini M, et al. Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease. Am J Cardiol 2010;105:288–92.
15. Jo SH, Koo BK, Park JS, et al. Prevention of radiocontrast medium-induced nephropathy using short-term high-dose simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial—a randomized controlled study. Am Heart J 2008;155:499.e1–8.
16. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.
17. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006;17:2937–44.
18. Standards of medical care in diabetes—2012. Diabetes Care 2012;35 Suppl 1:S11–63.
19. Di Giulio S, Meschini L, Triolo G. Dialysis outcome quality initiative (DOQI) guideline for hemodialysis adequacy. Int J Artif Organs 1998;21:757–61.
20. Zaytseva NV, Shamkhalova MS, Shestakova MV, et al. Contrast-induced nephropathy in patients with type 2 diabetes during coronary angiography: risk-factors and prognostic value. Diabetes Res Clin Pract 2009;86 Suppl 1:S63–9.
21. Wang XC, Fu XH, Wang YB, et al. Prediction of contrast-induced nephropathy in diabetics undergoing elective percutaneous coronary intervention: role of the ratio of contrast medium volume to estimated glomerular filtration rate. Chin Med J (Engl) 2011;124:892–6.
22. Layton JB, Kshirsagar AV, Simpson RJ Jr., et al. Effect of statin use on acute kidney injury risk following coronary artery bypass grafting. Am J Cardiol 2013;111:823–8.
23. Munoz MA, Maxwell PR, Green K, Hughes DW, Talbert RL. Pravastatin versus simvastatin for prevention of contrast-induced nephropathy. J Cardiovasc Pharmacol Ther 2011;16:376–9.
24. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE study): a prospective epidemiological survey. Lancet 2011;378:1231–43.
25. Praught ML, Shlipak MG. Are small changes in serum creatinine an important risk factor? Curr Opin Nephrol Hypertens 2005;14:265–70.
26. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 2004;15:1597–605.
27. Persson PB, Patzak A. Renal haemodynamic alterations in contrast medium-induced nephropathy and the benefit of hydration. Nephrol Dial Transplant 2005;20 Suppl 1:i2–5.
28. Kim SJ, Salem MR, Joseph NJ, Madayag MA, Cavallino RP, Crystal GJ. Contrast media adversely affect oxyhemoglobin dissociation. Anesth Analg 1990;71:73–6.
29. McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 2004;20:1501–10.
30. Brookhart MA, Solomon DH, Glynn RJ, Ridker PM. Effect of rosuvastatin on hemoglobin levels in patients with anemia and low-grade inflammation: a post hoc analysis of the JUPITER trial. J Clin Pharmacol 2011;51:1483–7.
31. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011;365:2078–87.

32. Scott LJ, Curran MP, Figgitt DP. Rosuvastatin: a review of its use in the management of dyslipidemia. Am J Cardiovasc Drugs 2004;4:117–38.
33. Shepherd J, Vidt DG, Miller E, Harris S, Blasetto J. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. Cardiology 2007;107:433–43.
34. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
35. Deo SH, Fisher JP, Vianna LC, et al. Statin therapy lowers muscle sympathetic nerve activity and oxidative stress in patients with heart failure. Am J Physiol Heart Circ Physiol 2012;303:H377–85.
36. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation 2004;109:III39–43.
37. Bonnet J, McPherson R, Tedgui A, et al. Comparative effects of 10-mg versus 80-mg Atorvastatin on high-sensitivity C-reactive protein in patients with stable coronary artery disease: results of the CAP (Comparative Atorvastatin Pleiotropic effects) study. Clin Ther 2008;30:2298–313.
38. Tsai YC, Hung CC, Kuo MC, et al. Association of hsCRP, white blood cell count and ferritin with renal outcome in chronic kidney disease patients. PLoS One 2012;7:e52775.
39. Fox ER, Benjamin EJ, Sarpong DF, et al. The relation of C-reactive protein to chronic kidney disease in African Americans: the Jackson Heart Study. BMC Nephrol 2010;11:1.
40. Shankar A, Sun L, Klein BE, et al. Markers of inflammation predict the long-term risk of developing chronic kidney disease: a population-based cohort study. Kidney Int 2011;80:1231–8.
41. Lee E, Ryan S, Birmingham B, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 2005;78:330–41.
42. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019–32.

Key Words: angiography ■ contrast medium ■ diabetes mellitus ■ kidney ■ statins.